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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/218,660	12/22/1998	EVAN C. UNGER	UNGR-1520	2775

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EXAMINER

SHARAREH, SHAHNAM J

ART UNIT

PAPER NUMBER

1617

DATE MAILED: 11/20/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/218,660

Applicant(s)

UNGER ET AL.

Examiner

Shahnam Sharareh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 September 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 3, 10, 100, 102, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337 and 347-356 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 29, 32. 6) ☐ Other: _____

Continuation of Disposition of Claims: Claims pending in the application are 3,10,100,102,127,194-200,203,210-228,294-300,303,310-329,331-337 and 347-356.

DETAILED ACTION

Amendment filed on September 3, 2002 has been entered. Claims 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356 are pending. Applicant is requested to provide a copy of all pending claims in response to this Office Action. Any rejection that is not addressed in this Office Action is considered obviated in view of the amendments.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

1. Applicant's arguments with respect to the priority ruling have been fully considered and are found persuasive. The effective priority date used for the examination of the instant application is May 1, 1996.

Claim Rejections - 35 USC § 103

Claims 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grinstaff US Patent 5,498,421 (Grinstaff) in view of Wallach US Patent 4,853,228 and Allen US Patent 5,620,689 and Ginsburg US Patent 5,656,442 (Ginsburg).

Applicant's arguments with respect to this rejection have been fully considered but are not found persuasive.

Applicant argues that the instant claims are now directed to such vesicles comprising membrane, which is substantially free of crosslinked proteins and polymer. As defined by the instant specification at page 18, line 8-10, "substantially" refers to a measurement of greater than about 50%.

Accordingly, in response to such argument, Examiner states that nowhere are the teachings of Grinstaff limited to more than 50% crossed linking between the employed proteins and polymers. In fact, such feature is a function of optimization of the stability of the vesicles. Accordingly, the combined teachings of Grinstaff, Wallace, Allen, and Ginsburg still render the instant claims obvious for the reasons of record.

New Grounds of Rejection

Claims 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace US Patent 4,853,228 (Wallace) and Allen US Patent 5,620,689 (Allan) in view of Schneider US Patent 5,643,553 (Schneider), Porter US Patent 5,648,098 (Porter) and Ginsburg US Patent 5,656,442 (Ginsburg).

The instant claims are now directed toward a formulation comprising targeted vesicles comprising one or more membranes encapsulating an internal void that contains a phospholipid and being substantially free of crossed-linked protein and polymers, a gas, a linking group and a targeting ligand, wherein the linking group is a hydrophilic polymer that is covalently bound to both the surface of the lipid vesicle and said targeting ligand and is selected from a group consisting of PEG, polypropylene glycol, polyvinylalcohol, PVP, and copolymers thereof.

The teachings of Wallach and Allen are previously described. Wallach and Allen primarily teach all the limitations of the instant formulation except that they do not employ gaseous perfluorocarbons in their compositions. Wallace discloses a composition comprising lipid vesicles such as liposomes, which are used to the delivery of diagnostic or therapeutic agents, (see col 5, lines 8-20). Wallach also teaches that such lipid vesicles may be conjugated to targeting ligands such as peptides to provide the advantage of in vivo site-specificity, (see col 4, lines 61+). Wallach teaches that the targeting ligand may be conjugated to the microspheres by covalent attachment of the targeting molecule to the amino group of PE via a spacer group of polyoxyethylene head groups, (see col 5, lines 1-7).

Similarly, Allen discloses a composition comprising vesicles such as liposomes which are used for delivery of diagnostic or therapeutic agents. Allen discloses that the liposomes shell may be formed from a phospholipid such as PE, (see entire col 6-8). Attached to the vesicle shell is a polymer chain in which a ligand (antibody) is covalently bound (see col 5-6; fig. 1, col 12, lines 29-34).

The use of gaseous perfluorocarbons in combination with drug delivery vesicles has been well established in the art. Schneider for example teaches liposomal composition comprising gas-filled microbubbles, wherein the microbubbles may contain various surfactant such as a microbubble shell forming phospholipid or more specifically PE, as well as, polymeric surfactants, such as PEG surfactants, (col 6, lines 25-64; claims 4-20).

Applicant's arguments with respect to the teachings of Schneider have been considered, but they are not accurate. Schneider explicitly teaches entrapped gas that becomes bound by said surfactant. Accordingly, the gas of Schneider is bounded or encapsulated by the phospholipid or other suitable surfactant (see col 13, lines 50-55). Schneider also teaches that targeting ligands (g.g, polypeptides, antibodies, etc..) may be bounded by the stabilizing surfactant layer of the microbubbles to provide site-specific targeting of the diagnostic or therapeutic microbubbles (see col 9, lines 10 +, example 11). Thus, Schneider teaches microbubbles, which comprise PE shell, combined with a PEG surfactant, which may be bound with a peptide targeting ligand. Schneider does not explicitly teach a perfluorinated gaseous liposome that is covalently bound to a targeting ligand via a PEG linker.

Porter teaches enhance drug activity when gaseous perfluorinated microbubbles are used in combination with the active drug.

Ginsberg discloses the synthetic alpha-amino acid containing chains of Lys-Gln-Ala-Gly-Asp-Val or RGD (col 33, lines 45-55) and that they specifically bind to fibrinogen of the platelet membrane glycoprotein complex IIb/IIIa receptor and that they can be used as a targeting ligand in an in vitro kit (abstract).

Since Wallace, Allen, Schneider, Porter and Ginsberg all disclose compositions comprising targeted lipid-coated vesicles for in vivo delivery of a diagnostic or therapeutic agents, they are viewed to be in the same field of endeavor.

Thus, although Wallace and Allen do not specifically employ gas within their liposomal moieties, it would have been obvious to one of ordinary skill in the art at the

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time of invention to employ gaseous moieties, as taught by Schneider and Porter, with the liposomes of Wallace and Allan, because as suggested by Schneider and Porter, the ordinary artisan would have expected to enhance the drug delivery of the agent of choice using gaseous vesicles that are attached to a suitable targeting agent, such as those taught by Ginsburg.

The ordinary skill in the art would have performed such modifications on Wallace and Allan's liposomes because he would have had a reasonable expectation of success in improving the targeting and specificity of the lipid vesicle's activity. Subsequently, methods of use and preparing such compositions would have also been obvious.

Conclusion

No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action, because the scope of the claims have been modified. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 703-308-1877. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.


RUSSELL TRAVERS
PRIMARY EXAMINER
GROUP 1200

ss

November 10, 2002